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(19) (CA) APPLICATION FOR CANADIAN PATENT (12)

(54) Linear Adhesion Inhibitors

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Notice: This application is as filed and may therefore contain an incomplete specification.



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**Abstract**

**Linear peptides of the formula I**

**X-A-Cys (R<sup>1</sup>) -B-Z**

**I,**

in which

A, B, R<sup>1</sup>, X and Z are as defined in Claim 1, are highly active inhibitors of the binding of the blood platelet integrin GP IIbIIIa ( $\alpha_{IIb}\beta_3$ ) to natural ligands and are suitable, *inter alia*, for the prophylaxis and for the treatment of circulatory disorders, thrombosis, myocardial infarction, coronary heart disease, arteriosclerosis, atherosclerosis, tumours and osteolytic diseases, and have a supporting effect in wound healing processes.

## Linear adhesion inhibitors

The invention relates to novel linear peptides of the formula I

X-A-Cys (R<sup>1</sup>) -B-Z

I,

5 which have been derived from the C-terminal sequence of echistatin and in which

X is H or Ac,

A is absent or is Asp or a peptide fragment selected from a group consisting of Ala-Asp, Thr-Ala-Asp, 10 Lys-Thr-Ala-Asp, Lys-Thr-Ala-Asn, Lys-Thr-Gly-Asp, Lys-Ala-Ala-Asp, Arg-Thr-Ala-Asp, Ser-Ala-Asp, Gln-Ser-Ala-Asp, Gly-Lys-Thr-Ala-Asp, Asn-Gly-Lys-Thr-Ala-Asp, Ile-Ser-Ala-Gly, Arg-Ser-Ala-Gly, Cys-Asn-Gly-Lys-Thr-Ala-Asp; 15 Tyr-Cys-Asn-Gly-Lys-Thr-Ala-Asp, Asp-Tyr-Cys-Asn-Gly-Lys-Thr-Ala-Asp, Gly-Lys-Thr-Cys-Asp, Asp-Asp-Tyr-Cys-Asn-Gly-Lys-Thr-Ala-Asp, Gly-Lys-Thr-Cys (Trt) -Asp,

20 Met-Asp-Asp-Tyr-Cys-Asn-Gly-Lys-Thr-Ala-Asp and Asp-Met-Asp-Asp-Tyr-Cys-Asn-Gly-Lys-Thr-Ala-Asp,

B is absent or is Ala, Arg, Asn, Asp, Cys, Gln, Glu, Gly, His, Ile, Leu, Lys, Met, Orn, Phe, 4-Hal-Phe, Pro, Ser, Thr, Trp, Tyr or Val or is an N-methylated 25 derivative of the amino acid residues mentioned, or is a peptide fragment selected from the group consisting of Pro-Arg, Pro-Arg-Asn, Pro-Arg-Asn-Pro, Pro-Arg-Asn-Pro-His, Pro-Arg-Asn-Pro-His-Lys, Pro-Arg-Asn-Pro-His-Lys-Gly,

30 Pro-Arg-Asn-Pro-His-Lys-Gly-Pro, Pro-Arg-Asn-Pro-His-Lys-Gly-Pro-Ala and Pro-Arg-Asn-Pro-His-Lys-Gly-Pro-Ala-Thr, in which only one of the residues A or B can be absent,

Z is OH, OR<sup>2</sup>, NH<sub>2</sub>, NHR<sup>2</sup> or N(R<sup>2</sup>)<sub>2</sub>,

35 R<sup>1</sup> is H, R<sup>2</sup>, Trt, Dpm or Bzl,

R<sup>2</sup> is alkyl of 1-6 carbon atoms,

Hal is F, Cl, Br or I

and

Ac is alkanoyl of 1-10 carbon atoms, aralkanoyl of 8-10 carbon atoms or aroyl of 7-11 carbon atoms, and to their physiologically acceptable salts.

5 Similar compounds are known from, for example, European Patent Application EP 0 406 428.

The object of the invention was to discover new compounds having valuable properties, especially those which can be used for the preparation of medicaments.

10 It has been found that the compounds of the formula I and their salts possess highly valuable properties. They act in particular as integrin inhibitors, in which context they particularly inhibit the interactions of  $\beta$ -integrin receptors with ligands. This action can be demonstrated by, for example, the method described by J.W. Smith et al. in J. Biol. Chem. 265, 12267-12271 (1990). In addition to this there are antiinflammatory effects. This action can also be demonstrated using methods known from the literature.

20 The compounds can be employed as active substances of medicaments in human and veterinary medicine, especially for the prophylaxis and for the treatment of circulatory disorders, thrombosis, myocardial infarction, coronary heart disease, arteriosclerosis, 25 atherosclerosis, inflammation, apoplexy, angina pectoris, tumours, osteolytic diseases, especially osteoporosis, angiogenesis and restenosis after angioplasty. In addition, they may have a supportive action in wound healing processes.

30 The abbreviations of amino acid residues given above and below denote the residues of the following amino acids:

Ala alanine

Arg arginine

35 Asn asparagine

Asp aspartic acid

Arg arginine

Cys cysteine

Gln glutamine

Glp pyroglutamine  
Glu glutaminic acid  
Gly glycine  
His histidine  
5 Ile isoleucine  
Leu leucine  
Lys lysine  
Met methionine  
Orn ornithine  
10 Phe phenylalanine  
Pro proline  
Ser serine  
Thr threonine  
Trp tryptophan  
15 Tyr tyrosine  
Val valine.

Furthermore, the abbreviations used below have  
the following definitions:

BOC tert-butoxycarbonyl  
20 Bzl benzyl  
CBZ benzyloxycarbonyl  
DCCI dicyclohexylcarbodiimide  
Dpm diphenylmethyl  
DMF dimethylformamide  
25 HDCI N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide  
hydrochloride  
Et ethyl  
Et<sub>2</sub>O diethyl ether  
Fmoc 9-fluorenylmethoxycarbonyl  
30 HOBT 1-hydroxybenzotriazole  
Me methyl  
MBHA 4-methyl-benzhydrylamine  
Mtr 4-methoxy-2,3,6-trimethylphenyl-sulfonyl  
OBu<sub>t</sub> tert-butyl ester  
35 OMe methyl ester  
OEt ethyl ester  
POA phenoxyacetyl  
TFA trifluoroacetic acid  
Trt trityl (triphenylmethyl).

Where the abovementioned amino acids may occur in two or more enantiomeric forms, then above and below, for example as a component of the compounds of the formula I, all of these forms and their mixtures too (e.g. the DL forms) are included, the three-letter code being the respective L form if the stereochemistry is not indicated.

The invention relates furthermore to a process for the preparation of a compound of the formula I according to Claim 1 or of one of its salts, characterized in that it is liberated from one of its functional derivatives by treatment with a solvolysing or hydrogenolysing agent  
or in that a peptide of formula II

15

X-M-OH

II

in which

M is an amino acid residue or peptide radical selected from a group consisting of A, A-Cys(R<sup>1</sup>), Ala, Thr, Thr-Ala, Lys, Lys-Thr, Lys-Thr-Ala, Lys-Thr-Ala-Gly, Gly, Gly-Lys, Gly-Lys-Thr, Gly-Lys-Thr-Ala, Gly-Lys-Thr-Cys(R<sup>1</sup>), Asn, Asn-Gly, Asn-Gly-Lys, Lys-Ala, Lys-Ala-Ala, Asn-Gly-Lys-Thr, Asn-Gly-Lys-Thr-Ala, Cys, Cys-Asn, Cys-Asn-Gly, Arg, Arg-Thr, Arg-Thr-Ala, Ser, Cys-Asn-Gly-Lys, Cys-Asn-Gly-Lys-Thr, Cys-Asn-Gly-Lys-Thr-Ala, Ser-Ala, Tyr, Tyr-Cys, Tyr-Cys-Asn, Tyr-Cys-Asn-Gly, Tyr-Cys-Asn-Gly-Lys, Gln, Gln-Ser, Gln-Ser-Ala, Tyr-Cys-Asn-Gly-Lys-Thr, Tyr-Cys-Asn-Gly-Lys-Thr-Ala, Asp, Asp-Tyr, Asp-Tyr-Cys, Asp-Tyr-Cys-Asn, Asp-Tyr-Cys-Asn-Gly, Asp-Tyr-Cys-Asn-Gly-Lys, Ile, Ile-Ser, Ile-Ser-Ala, Asp-Tyr-Cys-Asn-Gly-Lys-Thr, Arg-Ser, Arg-Ser-Ala, Asp-Tyr-Cys-Asn-Gly-Lys-Thr-Ala, Asp-Asp, Asp-Asp-Tyr, Asp-Asp-Tyr-Cys, Asp-Asp-Tyr-Cys-Asn, Asp-Asp-Tyr-Cys-Asn-Gly, Asp-Asp-Tyr-Cys-Asn-Gly-Lys, Asp-Asp-Tyr-Cys-Asn-Gly-Lys-Thr, Asp-Asp-Tyr-Cys-Asn-Gly-Lys-Thr-Ala, Met, Met-Asp, Met-Asp-Asp, Met-Asp-Asp-Tyr, Met-Asp-Asp-Tyr-Cys, Met-Asp-Asp-Tyr-Cys-Asn, Met-Asp-Asp-Tyr-Cys-Asn-Gly,

Met-Asp-Asp-Tyr-Cys-Asn-Gly-Lys,  
Met-Asp-Asp-Tyr-Cys-Asn-Gly-Lys-Thr,  
Met-Asp-Asp-Tyr-Cys-Asn-Gly-Lys-Thr-Ala, Asp-Met, Asp-Met-Asp,  
Asp-Met-Asp-Asp, Asp-Met-Asp-Asp-Tyr,  
Asp-Met-Asp-Asp-Tyr-Cys, Asp-Met-Asp-Asp-Tyr-Cys-Asn,  
Asp-Met-Asp-Asp-Tyr-Cys-Asn-Gly,  
Asp-Met-Asp-Asp-Tyr-Cys-Asn-Gly-Lys,  
Asp-Met-Asp-Asp-Tyr-Cys-Asn-Gly-Lys-Thr,  
Asp-Met-Asp-Asp-Tyr-Cys-Asn-Gly-Lys-Thr-Ala, A-Cys(R<sup>1</sup>)-Pro,  
A-Cys(R<sup>1</sup>)-Pro-Arg, A-Cys(R<sup>1</sup>)-Pro-Arg-Asn,  
A-Cys(R<sup>1</sup>)-Pro-Arg-Asn-Pro, A-Cys(R<sup>1</sup>)-Pro-Arg-Asn-Pro-His,  
A-Cys(R<sup>1</sup>)-Pro-Arg-Asn-Pro-His-Lys,  
A-Cys(R<sup>1</sup>)-Pro-Arg-Asn-Pro-His-Lys-Gly,  
A-Cys(R<sup>1</sup>)-Pro-Arg-Asn-Pro-His-Lys-Gly-Pro,  
A-Cys(R<sup>1</sup>)-Pro-Arg-Asn-Pro-His-Lys-Gly-Pro-Ala,

in which A and R<sup>1</sup> are as defined in Claim 1,

and

X is as defined but is not hydrogen if A and therefore  
M are absent, is reacted with an amino compound of  
the formula III

5

H-Q-Z

III,

in which

Z is as defined and

Q is an amino acid residue or peptide radical selected

10

from a group consisting of B, Cys(R<sup>1</sup>)-B,

Arg-Asn, Arg-Asn-Pro, Asn-Pro,

Arg-Asn-Pro-His, Asn-Pro-His, Pro-His, Arg-Asn-Pro-His-Lys,

Asn-Pro-His-Lys, Pro-His-Lys, His-Lys, Arg-Asn-Pro-His-Lys-Gly,

Asn-Pro-His-Lys-Gly, Pro-His-Lys-Gly, His-Lys-Gly, Lys-Gly,

Arg-Asn-Pro-His-Lys-Gly-Pro, Asn-Pro-His-Lys-Gly-Pro,

Pro-His-Lys-Gly-Pro, His-Lys-Gly-Pro, Lys-Gly-Pro, Gly-Pro,

Arg-Asn-Pro-His-Lys-Gly-Pro-Ala, Asn-Pro-His-Lys-Gly-Pro-Ala,

Pro-His-Lys-Gly-Pro-Ala, His-Lys-Gly-Pro-Ala, Lys-Gly-Pro-Ala,

Gly-Pro-Ala, Pro-Ala, Arg-Asn-Pro-His-Lys-Gly-Pro-Ala-Thr,

Asn-Pro-His-Lys-Gly-Pro-Ala-Thr, Pro-His-Lys-Gly-Pro-Ala-Thr,

His-Lys-Gly-Pro-Ala-Thr, Lys-Gly-Pro-Ala-Thr, Gly-Pro-Ala-Thr,

Pro-Ala-Thr, Ala-Thr, Gly-Asp-Cys(R<sup>1</sup>)-B, Thr-Gly-Asp-Cys(R<sup>1</sup>)-B,

Asp-Cys(R<sup>1</sup>)-B, Ala-Asp-Cys(R<sup>1</sup>)-B, Thr-Ala-Asp-Cys(R<sup>1</sup>)-B,  
Lys-Thr-Ala-Asp-Cys(R<sup>1</sup>)-B, Gly-Lys-Thr-Ala-Asp-Cys(R<sup>1</sup>)-B,  
Asn-Gly-Lys-Thr-Ala-Asp-Cys(R<sup>1</sup>)-B, Asn-Cys(R<sup>1</sup>)-B,  
Ala-Asn-Cys(R<sup>1</sup>)-B, Thr-Ala-Asn-Cys(R<sup>1</sup>)-B,  
Cys-Asn-Gly-Lys-Thr-Ala-Asp-Cys(R<sup>1</sup>)-B,  
Cys-Asn-Gly-Lys-Thr-Ala-Asp-Cys(R<sup>1</sup>)-B, Ala-Ala-Asp-Cys(R<sup>1</sup>)-B,  
Ser-Ala-Asp-Cys(R<sup>1</sup>)-B,  
Tyr-Cys-Asn-Gly-Lys-Thr-Ala-Asp-Cys(R<sup>1</sup>)-B, Gly-Cys(R<sup>1</sup>)-B,  
Ala-Gly-Cys(R<sup>1</sup>)-B, Ser-Ala-Gly-Cys(R<sup>1</sup>)-B, Cys(Trt)-Asp-Cys(R<sup>1</sup>)-B,  
Thr-Cys(Trt)-Asp-Cys(R<sup>1</sup>)-B, Lys-Thr-Cys(Trt)-Asp-Cys(R<sup>1</sup>)-B,  
Asp-Tyr-Cys-Asn-Gly-Lys-Thr-Ala-Asp-Cys(Trt)-B,  
Asp-Asp-Tyr-Cys-Asn-Gly-Lys-Thr-Ala-Asp-Cys(R<sup>1</sup>)-B or  
Met-Asp-Asp-Tyr-Cys-Asn-Gly-Lys-Thr-Ala-Asp-Cys(Trt)-B.

in which R<sup>1</sup> is as defined,

and/or in that a free mercapto, hydroxyl or amino group  
is alkylated

5 and/or a compound of the formula I is converted into one  
of its salts by treatment with an acid or base.

The residue A is preferably Ac-Asp, Ala-Asp,  
Thr-Ala-Asp, Lys-Thr-Ala-Asp, Ac-Lys-Thr-Ala-Asp,  
Gly-Lys-Thr-Cys-Asp, Gly-Lys-Thr-Cys(Trt)-Asp,  
10 Gly-Lys-Thr-Ala-Asp, Lys-Thr-Ala-Asn, Lys-Thr-Gly-Asp,  
Lys-Ala-Ala-Asp, Arg-Thr-Ala-Asp, Gly-Ser-Ala-Asp,  
Ac-Gln-Ser-Ala-Asp, Ile-Ser-Ala-Gly or Arg-Ser-Ala-Gly.

B is preferably not present or is, particularly  
preferably, Ala which may if desired be methylated,  
15 Pro, Pro-Arg, Pro-Arg-Asn, Pro-Arg-Asn-Pro,  
Pro-Arg-Asn-Pro-His, Pro-Arg-Asn-Pro-His-Lys,  
Pro - Arg - Asn - Pro - His - Lys - Gly or  
Pro-Arg-Asn-Pro-His-Lys-Gly-Pro-Ala-Thr, whereas X is  
preferably H or acetyl and Z is particularly preferably  
20 OH or NH<sub>2</sub>.

R<sup>1</sup> is particularly preferably a triphenylmethyl  
radical, whereas R<sup>2</sup> is preferably methyl but is also  
preferably, in addition, ethyl, propyl, butyl or tert-  
butyl.

25 The radical Ac is preferably acetyl but may also  
be formyl, propionyl, butyryl, isobutyryl, valeryl,  
isovaleryl or pivaloyl (trimethylacetyl), or furthermore

is preferably aroyl of 7-11 carbon atoms which is optionally substituted by one to three substituents, suitable substituents preferably being one of the following groups: alkyl, alkoxy, alkylthio, alkylsulfinyl or alkylsulfonyl having in each case 1-3, preferably 1 or 2, carbon atoms, methylenedioxy, and also OH, F, Cl, Br, I, NO<sub>2</sub>, NH<sub>2</sub>, alkylamino or dialkylamino having in each case 1-3, preferably 1 or 2, carbon atoms in the alkyl group. Individual preferred aroyl radicals are benzoyl, o-, m- or p-tolyl, o-, m- or p-methoxybenzoyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-dimethoxybenzoyl, 2,3,4-, 2,3,5-, 2,3,6-, 2,4,5-, 2,4,6- or 3,4,5-trimethoxybenzoyl, o-, m- or p-methylsulfonylbenzoyl, 2,3- or 3,4-methylenedioxybenzoyl, or 1- or 2-naphthoyl. Ac may also be aralkanoyl of 1-10 carbon atoms, for example phenylacetyl, 2- or 3-phenylpropionyl, 2-, 3- or 4-phenylbutyryl or 2- or 3-phenylisobutyryl.

Accordingly, the invention relates in particular to those compounds of the formula I in which at least one of the radicals or residues mentioned has one of the given meanings, in particular one of the meanings given as preferred.

Some preferred groups of compounds can be represented by the following subformulae Ia to Id, which conform to the formula I and in which the radicals, residues and parameters have the meaning given for formula I unless more closely specified, but in which

25 in Ia Cys(R<sup>1</sup>) is Cys(Trt) and B is Pro;

in Ib Cys(R<sup>1</sup>) is Cys(Trt) and B is

30 Pro-Arg-Asn-Pro-His-Lys-Gly-Pro-Ala-Thr;

in Ic Cys(R<sup>1</sup>) Cys(Trt) and

B is Pro-Arg, Pro-Arg-Asn-Pro,

Pro-Arg-Asn-Pro-His,

Pro-Arg-Asn-Pro-His-Lys or Pro-Arg-Asn-Pro-His-

35 Lys-Gly;

in Id Cys(R<sup>1</sup>) is Cys(Trt) and

A is Ala-Asp or Lys-Thr-Ala-Asp.

A further group of preferred compounds can be represented by subformulae Iaa to Ida, which otherwise

conform to the formula I and to the formulae Ia to Id, but in which additionally X is hydrogen and Z is OH or NH<sub>2</sub>.

5 The compounds of the formula I, and also the starting materials for their preparation, are otherwise prepared by known methods, as described in the literature (for example in the standard works such as Houben-Weyl, Methoden der organischen Chemie [Methods of Organic Chemistry], Georg-Thieme-Verlag, Stuttgart), under 10 reaction conditions which are known and suitable for the reactions mentioned. In this context use can also be made of known variants which are not mentioned here in any more detail.

15 If desired, the starting materials can also be formed in situ, so that they are not isolated from the reaction mixture but are reacted further straight away to give the compounds of the formula I.

20 The compounds of the formula I can be obtained by liberating them from their functional derivatives by solvolysis, in particular hydrolysis, or by hydrogenolysis.

25 Preferred starting materials for the solvolysis or hydrogenolysis are those which contain, instead of one or more free amino and/or hydroxyl groups, corresponding, protected amino and/or hydroxyl groups, preferably those which contain, instead of a hydrogen atom attached to a nitrogen atom, an amino-protective group, for example those which conform to the formula I but contain, instead of an NH<sub>2</sub> group, an NHR' group (in which R' is an amino-protective group, e.g. Fmoc, BOC or Cbz). 30

35 Further preferred starting materials are those which, instead of the hydrogen atom of a hydroxyl group, carry a hydroxy-protective group, for example those which conform to the formula I but which contain instead of a hydroxyphenyl group a R''O-phenyl group (in which R'' is a hydroxy-protective group).

It is also possible for two or more - identical or different - protected amino and/or hydroxyl groups to be present in the molecule of the starting material. If

the protective groups present are different from one another, then in many cases they can be removed selectively.

The term "amino-protective group" is generally known and relates to groups which are capable of protecting (blocking) an amino group against chemical reactions, but which are easily removable after the desired chemical reaction has been carried out at other sites of the molecule. In particular, such groups are typically unsubstituted or substituted acyl, aryl, aralkoxymethyl or aralkyl groups. Since the amino-protective groups are removed after the desired reaction (or reaction sequence), their nature and size is incidentally not critical; however, those of 1-20, in particular 1-8, carbon atoms are preferred. The term "acyl group" in the context of the present invention and the present compounds is to be understood in the widest sense. It includes acyl groups derived from aliphatic, araliphatic, aromatic or heterocyclic carboxylic acids or sulfonic acids, and also, in particular, alkoxy carbonyl, aryloxy carbonyl and - in particular - aralkoxycarbonyl groups. Examples of such acyl groups are alkanoyls such as acetyl, propionyl and butyryl; aralkanoyl such as phenyl-acetyl; acroyl such as benzoyl or tolyl; aryloxyalkanoyl such as POA; alkoxy carbonyl such as methoxycarbonyl, ethoxycarbonyl, 2,2,2-trichloroethoxycarbonyl, BOC, and 2-iodoethoxycarbonyl; aralkyloxycarbonyl such as CBZ ("carbobenzoxy"), 4-methoxybenzyloxycarbonyl and Fmoc; and arylsulfonyl such as Mtr. Preferred amino-protective groups are BOC and Mtr, and also CBZ, Fmoc, benzyl and acetyl.

The term "hydroxy-protective group" is likewise generally known and relates to groups which are capable of protecting a hydroxyl group against chemical reactions, but which are easily removable after the desired chemical reaction has been carried out at other sites of the molecule. Such groups are typically the abovementioned unsubstituted or substituted aryl, aralkyl or acyl groups, and also alkyl groups. The nature and

size of the hydroxy-protective groups is not critical since they are removed again after the desired chemical reaction or reaction sequence; groups of 1-20, in particular 1-10, carbon atoms are preferred. Examples of 5 hydroxy-protective groups include benzyl, p-nitrobenzoyl, p-toluenesulphonyl and acetyl, with benzyl and acetyl being particularly preferred. The COOH groups in aspartic acid and glutamic acid are preferably protected in the form of their tert-butyl esters (e.g. Asp (OBu<sub>2</sub>)).

10 The functional derivatives of the compounds of the formula I, to be used as starting materials, can be prepared by conventional methods of amino acid and peptide synthesis, as described in, for example, the standard works and patent applications mentioned, for 15 example by the solid-phase method of Merrifield (B.F. Gysin and R.B. Merrifield, J. Am. Chem. Soc. 94, 3102 et seq. (1972)) or more recent, modern variants which are derived therefrom and are known per se.

20 The liberation of the compounds of the formula I from their functional derivatives is carried out, depending on the protective group used, for example with strong acids, advantageously with TFA or perchloric acid, or else with other strong inorganic acids such as hydrochloric acid or sulphuric acid, strong organic carboxylic acids, such as trichloroacetic acid, or sulphonic acid 25 such as benzene- or p-toluenesulphonic acid. The presence of an additional inert solvent is possible but not always necessary. Suitable inert solvents are preferably organic acids, for example carboxylic acids such as acetic acid, ethers such as tetrahydrofuran or dioxane, amides such as 30 DMF, halogenated hydrocarbons such as dichloromethane, and also alcohols such as isopropanol, sec- or tert-butanol, and, in individual cases, methanol or ethanol, and also water. Mixtures of the abovementioned solvents 35 are also suitable. TFA is preferably used in excess without the addition of a further solvent, while perchloric acid is preferably used in the form of a mixture of acetic acid and 70% strength perchloric acid in the ratio 9:1. The reaction temperatures for the cleavage are

advantageously between about 0 and about 50°, preferably between 15 and 30° (room temperature).

For example, the groups BOC, But, OBut, Trt and Mtr can be removed preferably with TFA in dichloromethane 5 or with about 3 to 5 n HCl in dioxane at 0-30°, in which context auxiliary reagents such as anisole, thiophenol or thioanisole may have a favourable effect on the reaction. The removal of the Fmoc group is carried out, for example, using an about 5 to 50% strength solution of 10 dimethylamine, diethylamine, morpholine or piperidine in DMF at 0-30°. It is possible here to remove the Trt group selectively from amino acid residues to which it is attached via oxygen, while leaving a Trt group attached via sulphur in the molecule. Likewise, a Trt residue can 15 be introduced subsequently by attaching it preferably to nucleophilic sulphur, while OH groups in the side chain are not substituted.

Protective groups which can be removed by hydrogenolysis (e.g. CBZ or benzyl) can be removed, for 20 example, by treatment with hydrogen in the presence of a catalyst (e.g. a noble metal catalyst such as palladium, advantageously on a support such as charcoal). In this context, suitable solvents are those given above, particular examples being alcohols such as methanol or 25 ethanol, ethers such as THF, carboxylic acids such as acetic acid, water, or amides such as DMF. The hydrogenolysis is generally carried out at temperatures between about 0 and 100° and pressures of between about 1 and 200 bar, preferably at 20-30° and 1-10 bar. For example, 30 hydrogenolysis of the CBZ group is favourably achieved over 5 to 10% Pd-C in methanol or with ammonium formate (instead of H<sub>2</sub>) over Pd-C in water/DMF at 20-30°.

Compounds of the formula I can also be obtained by reacting a compound of the formula II with an amino 35 compound of the formula III under condensing conditions which are known per se for peptide syntheses, and are described, for example, in Houben-Weyl, loc. cit., vol. 15/II, pp. 1-806 (1974).

The reaction occurs preferably in the presence of

a dehydrating agent, for example a carbodiimide such as DCCI or EDCI, and also propanephosphonic anhydride (cf. Angew. Chem. 92, 129 (1980)), diphenylphosphoryl azide or 2-ethoxy-N-ethoxycarbonyl-1,2-dihydroquinoline in an inert solvent, for example a halogenated hydrocarbon such as dichloromethane, an ether such as tetrahydrofuran or dioxane, an amide such as DMF or dimethylacetamide, a nitrile such as acetonitrile, or in mixtures of these solvents, at temperatures of between about -10 and 40°, preferably between 0 and 30°.

Instead of II it is also possible to employ suitable reactive derivatives of these substances in the reaction, for example those in which reactive groups are blocked intermediately by protective groups. The amino acid derivatives II can be used, for example, in the form of their activated esters which, advantageously, are formed *in situ* by, for example, addition of HOBt or N-hydroxysuccinimide. However, they can also be employed in the form of their mixed anhydrides, which can be prepared using carboxylic acid halides such as pivaloyl chloride or isobutyloxycarbonyl chloride.

The starting substances of the formula II are generally novel. They can be prepared by known methods, for example by the methods given above for peptide synthesis and for the removal of protective groups.

In general, synthesis proceeds by first preparing protected peptide esters of the formula R'-M'-OR", e.g. BOC-M-OMe or Fmoc-M-OBu. These are hydrolysed to give acids of the formula R'-M-OH, for example BOC-M-OH or Fmoc-M-OH, which are then condensed with a compound of the formula III which, if desired, is likewise provided with appropriate protective groups at positions in which reaction is not to take place.

In the case of compounds of the formula III, peptide esters of the formula R'-Q-Z'-R", such as BOC-Q-Z'-OMe or Fmoc-Q-Z'-OMe, where Z' is -NH- or -O-, are likewise synthesized and then, before carrying out the condensation for the preparation of compounds of the formula I, the protective group R' is removed in a known

manner, Fmoc being removed, for example, by treatment with a piperidine/DMF solution.

It is particularly advantageous to use the more recent methods of peptide synthesis according to modified 5 Merrifield techniques and using peptide synthesis instruments, as are described, for example, in Peptides, Proc. 8th Am. Pept. Symp., Eds. V. Hruby and D.H. Rich, Pierce Comp. III, p. 73-77 (1983) by A. Jonczyk and J. Meinenhofer (Fmoc strategy), or the techniques given 10 in Angew. Chem. 104, 375-391 (1992). Such methods are known per se.

A base of formula I can be converted into the relevant acid addition salt using an acid. Acids which are particularly suitable for this reaction are those 15 which give physiologically acceptable salts. For instance, examples of inorganic acids which can be used are sulphuric acid, nitric acid, hydrohalic acids such as hydrochloric acid or hydrobromic acid, phosphoric acids such as orthophosphoric acid, sulfamic acid, and also 20 organic acids, in particular aliphatic, alicyclic, araliphatic, aromatic or heterocyclic mono- or polybasic carboxylic, sulphonic or sulphuric acids, for example formic acid, acetic acid, propionic acid, pivalic acid, diethylacetic acid, malonic acid, succinic acid, pimelic 25 acid, fumaric acid, maleic acid, lactic acid, tartaric acid, malic acid, benzoic acid, salicylic acid, 2- or 3-phenylpropionic acid, citric acid, gluconic acid, ascorbic acid, nicotinic acid, isonicotinic acid, methane- or ethanesulphonic acid, ethanesulphonic acid, 2-hydroxyethanesulphonic acid, benzenesulphonic acid, p-toluene- 30 sulphonic acid, naphthalene-mono- and -disulphonic acids, and laurylsulphuric acid. Salts with acids which are not physiologically acceptable, for example picrates, can be used to isolate and/or purify the compounds of the 35 formula I.

Alternatively, an acid of the formula I can be converted into one of its physiologically acceptable metal salts or ammonium salts by reaction with a base. In this case particularly suitable salts are the sodium,

potassium, magnesium, calcium and ammonium salts, and also substituted ammonium salts, for example the dimethyl-, diethyl- or diisopropylammonium salts, monooctanol-, diethanol- or triethanolammonium salts, 5 cyclohexyl- and dicyclohexylammonium salts, dibenzyl-ethylenediammonium salts, and also salts with, for example, N-methyl-D-glucamine or with arginine or lysine.

10 The novel compounds of the formula I can be used, furthermore, as integrin ligands for the preparation of columns for affinity chromatography, for the isolation of integrins.

In this context the ligand, i.e. a peptide derivative of the formula I, is coupled covalently to a polymer support via anchor functions.

15 Suitable polymer support materials are the solid, polymeric phases which are known per se in peptide chemistry and preferably have hydrophilic properties, examples being crosslinked polysugars such as cellulose, Sepharose or Sephadex®, acrylamides, polymers based on 20 polyethylene glycol or Tentakel® polymers.

Suitable anchor functions which are attached to the polymer supports are preferably linear alkylene chains of 2-12 carbon atoms, in which one end is attached directly to the polymer and the other end carries a 25 functional group such as, for example, hydroxyl, amino, mercapto, maleimido or -COOH, and which are suitable for linking with the C- or N-terminal section of the respective peptide.

30 In this context it is possible for the peptide to be attached directly or, if desired, via a second anchor function to the anchor of the polymer. It is also possible for peptides containing amino acid residues having functionalized side chains to be attached via the latter to the anchor function of the polymer.

35 Moreover, it is possible for certain amino acid residues which are a component of the peptides of the formula I to have their side chains modified such that they are available for anchoring, via SH, OH, NH<sub>2</sub> or COOH groups for example, with the anchor of the polymer.

It is possible in this case to use amino acids which are not customary, for example phenylalanine derivatives which carry a mercapto, hydroxyl, amino or carboxyalkyl chain in position 4 of the phenyl ring, the functional group being at the end of the chain.

5 Examples of amino acid residues whose side chain can be used directly as an anchor function are Lys, Orn, Arg, Asp, Asn, Glu, Gln, Ser, Thr, Cys or Tyr.

10 Examples of N-terminal anchors are radicals such as, for example,  $-\text{CO}-\text{C}_n\text{H}_{2n}-\text{NH}_2$ ,  $-\text{CO}-\text{C}_n\text{H}_{2n}-\text{OH}$ ,  $-\text{CO}-\text{C}_n\text{H}_{2n}-\text{SH}$  or  $-\text{CO}-\text{C}_n\text{H}_{2n}-\text{COOH}$  where  $n = 2-12$ , the length of the alkylene chain not being critical; it is also possible, if desired, for this chain to be replaced in whole or in part by, for example, appropriate aryl or alkylaryl radicals.

15 Examples of possible C-terminal anchors are  $-\text{O}-\text{C}_n\text{H}_{2n}-\text{SH}$ ,  $-\text{O}-\text{C}_n\text{H}_{2n}-\text{OH}$ ,  $-\text{O}-\text{C}_n\text{H}_{2n}-\text{NH}_2$ ,  $-\text{O}-\text{C}_n\text{H}_{2n}-\text{COOH}$ ,  $-\text{NH}-\text{C}_n\text{H}_{2n}-\text{SH}$ ,  $-\text{NH}-\text{C}_n\text{H}_{2n}-\text{OH}$ ,  $-\text{NH}-\text{C}_n\text{H}_{2n}-\text{NH}_2$  or  $-\text{NH}-\text{C}_n\text{H}_{2n}-\text{COOH}$ ,  $n$  and the alkylene chain both being subject to what was stated in the previous paragraph.

20 The N- and C-terminal anchors can also be used as the anchor component for an amino acid residue side chain which is already functionalized. Examples of suitable amino acid residues in this case are Lys( $\text{CO}-\text{C}_3\text{H}_{10}-\text{NH}_2$ ), Asp( $\text{NH}-\text{C}_2\text{H}_4-\text{COOH}$ ) or Cys( $\text{C}_2\text{H}_4-\text{NH}_2$ ), the anchor always being attached to the functional group of the side chain.

25 The preparation of the materials for affinity chromatography is carried out under conditions as are conventional and known per se for the condensation of amino acids and which have already been described in the section relating to the preparation of the compounds of the formula I, and which are described in Pierce, Immuno Technology Catalog & Handbook (1990).

30 The novel compounds of the formula I, and their physiologically acceptable salts, may be used for preparing pharmaceutical preparations by bringing them into a suitable dosage form together with at least one excipient or auxiliary and, if desired, together with one or more additional active substances. The formulations

thus obtained can be employed as medicaments in human or veterinary medicine. Suitable substances as excipients are organic or inorganic substances which are suitable for enteral (e.g. oral or rectal), parenteral (e.g. 5 intravenous injection) or local (e.g. topical, dermal, ophthalmic or nasal) administration or for administration in the form of an inhalation spray and which do not react with the novel compounds, examples being water or aqueous isotonic saline solution, lower alcohols, vegetable oils, 10 benzyl alcohols, polyethylene glycols, glycerol triacetate and other fatty acid glycerides, gelatin, soya lecithin, carbohydrates such as lactose or starch, magnesium stearate, talc, cellulose and petroleum jelly. Oral administration forms are, in particular, tablets, 15 film-coated tablets, capsules, syrups, juices or drops; coated tablets and capsules with gastric juice-resistant coatings or capsule casings are of special interest. Suppositories can be used for rectal administration, while parenteral administration employs solutions, 20 preferably oily or aqueous solutions, and also suspensions, emulsions or implants. Examples of forms suitable for topical administration are solutions, which may be used in the form of eye drops, and further examples are suspensions, emulsions, creams, ointments or 25 compresses. For administration as an inhalation spray, sprays can be used which contain the active substance either dissolved or suspended in a propellant gas or propellant gas mixture (e.g. CO<sub>2</sub> or fluorochloro-hydrocarbons or appropriate substitutes). In this case 30 the active substance is expediently used in micronized form, it being possible for one or more additional, physiologically tolerated solvents to be present, e.g. ethanol. Inhalation solutions can be administered using customary inhalers. The novel compounds may also be 35 lyophilized and the resulting lyophilizates can be used, for example, for producing injection preparations. In this context the injections may be given as a bolus or as a continuous infusion (e.g. intravenous, intramuscular, subcutaneous or intrathecal). The given formulations can

be sterilized and/or may contain auxiliaries, such as preservatives, stabilizers and/or wetting agents, emulsifiers, salts for influencing the osmotic pressure, buffer substances, colorants and/or fragrances. They may, 5 if desired, also contain one or more further active substances, for example one or more vitamins.

The substances according to the invention can generally be administered in analogy to other known and commercially available peptides, but in particular in 10 analogy to the compounds described in US-A-4 472 305, preferably in dosages of between about 0.05 and 500 mg, in particular between 0.5 and 100 mg, per dosage unit. The daily dose is preferably between about 0.01 and 15 2 mg/kg of body weight. The specific dose for each particular patient depends, however, on a wide variety of factors, for example on the effectiveness of the specific compound employed, on the age, body weight, general state of health, gender, on the diet, on the time and route of administration, on the rate of excretion, on the 20 combination of medicaments and the severity of the respective disease to which the therapy is applied. Parenteral administration is preferred.

All temperatures above and below are given in °C. In the examples which follow, "customary work-up" means: 25 water is added if necessary, the mixture is neutralized, extracted with dichloromethane, the phases are separated, the organic phase is dried over sodium sulphate, filtered, concentrated by evaporation and purified by chromatography on silica gel and/or crystallization. 30 "Customary purification" denotes that the peptide is precipitated from TFA/CH<sub>2</sub>Cl<sub>2</sub>, using diethyl ether, after which gel filtration is carried out in aqueous buffers and/or ion exchange chromatography is carried out. R<sub>t</sub> = retention time (minutes) for HPLC on Lichrosorb RP<sup>®</sup> 35 select B(250-4.7 mm) column, eluent: 0.3% TFA in water; isopropanol gradient of 0-80 vol% in 50 min at a flow rate of 1 ml/min, and detection at 215 nm. M<sup>\*</sup> = molecular peak in the mass spectrum obtained by the "fast atom bombardment" (FAB) method, generally representing M<sup>\*</sup> + H,

in other words the mass of the respective compound increased by 1 mass unit. DMPP resin is 4-(2',4'-dimethoxyphenylhydroxymethyl)phenoxy resin, a super-acid-labile resin which permits the synthesis of peptides with protected side chains.

5

Example 1

0.6 g of Fmoc-Pro-OH is dissolved in 100 ml of dichloromethane, 1.2 equivalents of Wang resin (p-benzyl-oxybenzyl alcohol resin) are added, and the mixture is stirred at room temperature for 12 hours. After removal of the solvent Fmoc-Pro-Wang resin is obtained. In a peptide synthesizer Fmoc-Cys(Trt)-OH is condensed with H-Pro-Wang resin [liberation from Fmoc-Pro-Wang resin using piperidine/DMF (20% strength)], using a threefold excess of the protected cysteine. The coupling is carried out at room temperature in DCCI/HOBt, to give Fmoc-Cys(Trt)-Pro-Wang resin. Subsequent treatment with piperidine/DMF (20% strength) again gives H-Cys(Trt)-Pro-Wang resin.

10

Example 2

In analogy to Example 1 and starting from Fmoc-Gly-DMPP resin, by condensation with Fmoc-Ala-OH, Fmoc-Ser(But)-OH and Fmoc-Ile-OH in the sequence given in a peptide synthesizer (continuous flow principle), after carrying out the following steps:

- liberation of H-Gly-DMPP resin using piperidine/DMF (20%)
- washing with dimethylacetamide (DMA)
- reaction with Fmoc-Ala-OH in DCCI/HOBt at room temperature
- washing and treatment with piperidine/DMF (20%)
- coupling of the resulting H-Ala-Gly-DMPP resin with Fmoc-Ser(But)-OH
- washing and treatment of the resulting Fmoc-Ser(But)-Ala-Gly-DMPP resin with  $\text{CF}_3\text{SO}_3\text{H}/\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$ ,

15

20

25

Fmoc-Ser(But)-Ala-Gly-OH is obtained.

Example 3

By analogy with Example 2, starting from Fmoc-Asn(Trt)-DMPP resin and after carrying out the appropriate reaction steps,

5 Fmoc-Lys(Boc)-Thr(But)-Ala-Asn(Trt)-OH  
is obtained by coupling with Fmoc-Ala-OH, Fmoc-Thr(But)-OH and Fmoc-Lys(Boc)-OH in the specified sequence.

10 Example 4

By analogy with Example 2, starting from Fmoc-Asp(OBut)-DMPP resin and after carrying out the appropriate reaction steps, the following are obtained:

15 Fmoc-Lys(Boc)-Thr(But)-Gly-Asp(OBut)-OH  
by coupling with Fmoc-Gly-OH, Fmoc-Thr(But)-OH and Fmoc-Lys(Boc)-OH in the specified sequence;  
Fmoc-Lys(Boc)-Ala-Ala-Asp(OBut)-OH  
by coupling with Fmoc-Ala-OH, Fmoc-Ala-OH and Fmoc-Lys(Boc)-OH in the specified sequence;  
20 Fmoc-Arg(Mtr)-Thr(But)-Ala-Asp(OBut)-OH  
by coupling with Fmoc-Ala-OH, Fmoc-Thr(But)-OH and Fmoc-Arg(Mtr)-OH in the specified sequence;  
Fmoc-Ser(But)-Ala-Asp(OBut)-OH  
by coupling with Fmoc-Ala-OH and Fmoc-Ser(But)-OH in the  
25 specified sequence;  
Fmoc-Lys(Boc)-Thr(But)-Ala-Asp(OBut)-OH  
by coupling with Fmoc-Ala-OH, Fmoc-Thr(But)-OH and Fmoc-Lys(Boc)-OH in the specified sequence;  
Fmoc-Gln(Trt)-Ser(But)-Ala-Asp(OBut)-OH  
30 by coupling with Fmoc-Ala-OH, Fmoc-Ser(But)-OH and Fmoc-Gln(Trt)-OH in the specified sequence.

Example 5

0.4 g of H-Cys(Trt)-Pro-Wang resin are condensed in a peptide synthesizer (continuous flow principle) with  
35 Fmoc-Lys(Boc)-Thr(But)-Ala-Asn(Trt)-OH, using a three-fold excess of the Fmoc peptide. The coupling is carried

out at room temperature in DCCI/HOBt, to give Fmoc-Lys(Boc)-Thr(But)-Ala-Asn(Trt)-Cys(Trt)-Pro-Wang resin. Subsequent treatment with TFA/CH<sub>2</sub>Cl<sub>2</sub>, followed by removal of the Fmoc group with piperidine/DMF (20%) gives

5 H-Lys-Thr-Ala-Asn-Cys(Trt)-Pro-OH.

The following are obtained analogously by condensation of H-Cys(Trt)-Pro-Wang resin with Fmoc-Lys(Boc)-Thr(But)-Ala-Asp(Trt)-OH:

H-Lys-Thr-Ala-Asp-Cys(Trt)-Pro-OH; Rt = 28.9; M<sup>+</sup> =

10 876;

with Fmoc-Lys(Boc)-Ala-Ala-Asp(Trt)-OH:

H-Lys-Ala-Ala-Asp-Cys(Trt)-Pro-OH;

with Fmoc-Arg(Mtr)-Thr(But)-Ala-Asp(Trt)-OH:

H-Arg-Thr-Ala-Asp-Cys(Trt)-Pro-OH;

15 with Fmoc-Ser(But)-Ala-Asp(Trt)-OH:

H-Ser-Ala-Asp-Cys(Trt)-Pro-OH;

with Fmoc-Gln(Trt)-Ser(But)-Ala-Asp(Trt)-OH:

H-Gln-Ser-Ala-Asp-Cys(Trt)-Pro-OH;

with Fmoc-Glp-Ser(But)-Ala-Asp(Trt)-OH:

20 H-Glp-Ser-Ala-Asp-Cys(Trt)-Pro-OH;

with Fmoc-Lys(Boc)-Thr(But)-Ala-Asp(Trt)-OH:

H-Lys-Thr-Ala-Asp-Cys(Trt)-Pro-OH;

with Fmoc-Ile-Ser(But)-Ala-Gly-OH:

H-Ile-Ser-Ala-Gly-Cys(Trt)-Pro-OH;

25 with Fmoc-Arg(Mtr)-Ser(But)-Ala-Gly-OH:

H-Arg-Ser-Ala-Gly-Cys(Trt)-Pro-OH;

with Fmoc-Lys(Boc)-Gly-Gly-Asp(Trt)-OH:

H-Lys-Gly-Gly-Asp-Cys(Trt)-Pro-OH.

#### Example 6

30 By analogy with Example 5, starting from H-Cys(Trt)-Wang resin and by condensation with Fmoc-Lys(Boc)-Thr(But)-Ala-Asp(OBut)-OH in a peptide synthesizer, Fmoc-Lys(Boc)-Thr(But)-Ala-Asp(OBut)-Cys(Trt)-Wang resin is obtained which, after treatment 35 with TFA/CH<sub>2</sub>Cl<sub>2</sub>, followed by removal of the Fmoc group using piperidine/DMF (20%) and conventional purification gives H-Lys-Thr-Ala-Asp-Cys(Trt)-OH; Rt = 28.8; M<sup>+</sup> = 779.

Example 7

1.2 g of BOC-Thr(But)-Ala-Asp(Obut)-Cys-Pro-Arg(Mtr)-OH are dissolved in a mixture of 150 ml of dichloromethane and 20 ml of DMF, the mixture is cooled to 0°, and then 0.5 g of DCCI, 0.3 g of HOBt, 0.23 ml N-methylmorpholine and one equivalent of H-Asn(Trt)-Pro-His(Trt)-Lys(Boc)-GlyPro-Ala-Thr(But)-OMe [both peptides can be obtained by methods of the modified Merrifield technique] are added. The mixture is stirred at 0°C for 20 hours and at room temperature for 6 hours. The reaction mixture is concentrated, treated with an ion exchanger and placed in an aqueous NaHCO<sub>3</sub> solution. The product which precipitates is filtered off with suction and washed with water. After crystallization from ethyl acetate/petroleum ether, BOC-Thr(But)-Ala-Asp(Obut)-Cys-Pro-Arg(Mtr)-Asn(Trt)-Pro-His(Trt)-Lys(Boc)-Gly-Pro-Ala-Thr(But)-OMe is obtained.

The following are obtained analogously by condensation

of BOC-Gly-Lys(Boc)-Thr(But)-Cys(Trt)-Asp(Obut)-OH with H-Cys(Trt)-Pro-Arg(Mtr)-Asn(Trt)-Pro-His(Trt)-Lys(Boc)-Gly-Pro-Ala-Thr(But)-OMe:

BOC-Gly-Lys(Boc)-Thr(But)-Cys(Trt)-Asp(Obut)-Cys(Trt)-Pro-Arg(Mtr)-Asn(Trt)-Pro-His(Trt)-Lys(Boc)-Gly-Pro-Ala-Thr(But)-OMe;

of BOC-Lys(Boc)-Thr(But)-Ala-Asp(Obut)-Cys(Trt)-OH with H-Pro-Arg(Mtr)-Asn(Trt)-Pro-His(Trt)-Lys(Boc)-Gly-OMe:

BOC-Lys(Boc)-Thr(But)-Ala-Asp(Obut)-Cys(Trt)-Pro-Arg(Mtr)-Asn(Trt)-Pro-His(Trt)-Lys(Boc)-Gly-OMe.

Example 8

0.3 g of BOC-Thr(But)-Ala-Asp(Obut)-Cys-Pro-Arg(Mtr)-Asn(Trt)-Pro-His(Trt)-Lys(Boc)-Gly-Pro-Ala-Thr(But)-OMe is dissolved in 30 ml of methanol; 1.5 ml of 2N NaOH solution are added and the mixture is stirred at 25° for 4 hours. After removal of the solvent the residue is taken up in water, the pH is adjusted to 3 by adding diluted HCl, and the product is extracted with ethyl acetate. The extract is dried over Na<sub>2</sub>SO<sub>4</sub>. After removal

of the solvent BOC-Thr(But)-Ala-Asp(Obut)-Cys-Pro-Arg(Mtr)-Asn(Trt)-Pro-His(Trt)-Lys(Boc)-Gly-Pro-Ala-Thr(But)-OH is obtained, which is taken up in 20 ml of 2N HCl in dioxane and stirred at room temperature for 2 hours. The 5 reaction mixture is concentrated to dryness and the residue is taken up in TFA/CH<sub>2</sub>Cl<sub>2</sub>, precipitated with Et<sub>2</sub>O and purified by RP-HPLC, to give H-Thr-Ala-Asp-Cys-Pro-Arg-Asn-Pro-His-Lys-Gly-Pro-Ala-Thr-OH; Rt = 12.6; M<sup>+</sup> = 1465.

10 The following are obtained analogously by removal of the protective groups, starting from the compounds of Example 7:

H-Gly-Lys-Thr-Cys-Asp-Cys-Pro-Arg-Asn-Pro-His-Lys-Gly-Pro-Ala-Thr-OH; Rt = 13.1; M<sup>+</sup> = 1681;

15 H-Lys-Thr-Ala-Asp-Cys-Pro-Arg-Asn-Pro-His-Lys-Gly-OH.

#### Example 9

By analogy with Example 1, starting from H-Thr(But)-Wang resin and by condensation with Fmoc-Ala-OH, Fmoc-Pro-OH, Fmoc-Gly-OH, Fmoc-Lys(Boc)-OH, Fmoc-His(Trt)-OH and Fmoc-Pro-OH in the specified sequence in a peptide synthesizer (continuous flow principle) after repeating the steps indicated above, Fmoc-Pro-His(Trt)-Lys(Boc)-Gly-Pro-Ala-Thr(But)-Wang resin is obtained, which is treated again with piperidine/DMF (20%) to give 25 H-Pro-His(Trt)-Lys(Boc)-Gly-Pro-Ala-Thr(But)-Wang resin.

#### Example 10

By analogy with Example 1, starting from H-Gly-Wang resin and by condensation with Fmoc-Lys(Boc)-OH, Fmoc-His(Trt)-OH and Fmoc-Pro-OH, in the specified 30 sequence in a peptide synthesizer (continuous flow principle) after repeating the steps indicated above, Fmoc-Pro-His(Trt)-Lys(Boc)-Gly-Wang resin is obtained, which is then treated again with piperidine/DMF (20%) to give H-Pro-His(Trt)-Lys(Boc)-Gly-Wang resin.

#### Example 11

35 By analogy with Example 2, starting from

Fmoc-Asn(Trt)-Wang resin and after carrying out the appropriate reaction steps

5 Fmoc-Ala-Asp(Obut)-Cys(Trt)-Pro-Arg(Mtr)-Asn(Trt)-OH is obtained by coupling with Fmoc-Arg(Mtr)-OH, Fmoc-Pro-  
OH, Fmoc-Cys(Trt)-OH, Fmoc-Asp(Obut)-OH and Fmoc-Ala-OH in the specified sequence.

Analogously, starting from Fmoc-Asn(Trt)-Wang resin,

10 Fmoc-Lys(Boc)-Thr(But)-Ala-Asp(Obut)-Cys(Trt)-Pro-  
Arg(Mtr)-Asn(Trt)-OH is obtained by coupling with Fmoc-Arg(Mtr)-OH, Fmoc-Pro-  
OH, Fmoc-Cys(Trt)-OH, Fmoc-Asp(Obut)-OH, Fmoc-Ala-OH,  
Fmoc-Thr(But)-OH and Fmoc-Lys(Boc)-OH in the specified sequence;

15 Fmoc-Gly-Lys(Boc)-Thr(But)-Cys(Trt)-Asp(Obut)-  
Cys(Trt)-Pro-Arg(Mtr)-Asn(Trt)-OH is obtained by coupling with Fmoc-Arg(Mtr)-OH, Fmoc-Pro-  
OH, Fmoc-Cys(Trt)-OH, Fmoc-Asp(Obut)-OH, Fmoc-Cys(Trt)-  
OH, Fmoc-Thr(But)-OH, Fmoc-Lys(Boc)-OH and Fmoc-Gly-OH in  
20 the specified sequence;

Fmoc-Ala-Asp(Obut)-Cys(Trt)-Pro-Arg(Mtr)-Asn(Trt)-OH is obtained by coupling with Fmoc-Arg(Mtr)-OH, Fmoc-Pro-  
OH, Fmoc-Cys(Trt)-OH, Fmoc-Asp(Obut)-OH and Fmoc-Ala-OH in the specified sequence;

25 Fmoc-Gly-Lys(Boc)-Thr(But)-Ala-Asp(Obut)-Cys(Trt)-  
Pro-Arg(Mtr)-Asn(Trt)-OH is obtained by coupling with Fmoc-Arg(Mtr)-OH, Fmoc-Pro-  
OH, Fmoc-Cys(Trt)-OH, Fmoc-Asp(Obut)-OH, Fmoc-Ala-OH,  
Fmoc-Thr(But)-OH, Fmoc-Lys(Boc)-OH and Fmoc-Gly-OH in the  
30 specified sequence; and

Fmoc-Thr(But)-Ala-Asp(Obut)-Cys(Trt)-Pro-Arg(Mtr)-  
Asn(Trt)-OH is obtained by coupling with Fmoc-Arg(Mtr)-OH, Fmoc-Pro-  
OH, Fmoc-Cys(Trt)-OH, Fmoc-Asp(Obut)-OH, Fmoc-Ala-OH and  
35 Fmoc-Thr(But)-OH in the specified sequence.

Example 12

By analogy with Example 5, by condensation of

H-Pro-His(Trt)-Lys(Boc)-Gly-Pro-Ala-Thr(But)-Wang resin with Fmoc-Ala-Asp(Obut)-Cys(Trt)-Pro-Arg(Mtr)-Asn(Trt)-OH, Fmoc-Ala-Asp(Obut)-Cys(Trt)-Pro-Arg(Mtr)-Asn(Trt)-

5 Pro-His(Trt)-Lys(Boc)-Gly-Pro-Ala-Thr(But)-Wang resin is

obtained. Subsequent treatment with TFA/CH<sub>2</sub>Cl<sub>2</sub>, followed by removal of the Fmoc group with piperidine/DMF (20%) gives:

H-Ala-Asp-Cys(Trt)-Pro-Arg-Asn-Pro-His-Lys-Gly-Pro-Ala-Thr-OH; Rt = 25.6; M<sup>+</sup> = 1606.

10 The following are obtained analogously by condensation

of H-Pro-His(Trt)-Lys(Boc)-Gly-Pro-Ala-Thr(But)-Wang resin with Fmoc-Lys(Boc)-Thr(But)-Ala-Asp(Obut)-Cys(Trt)-Pro-Arg(Mtr)-Asn(Trt)-OH:

15 H-Lys-Thr-Ala-Asp-Cys(Trt)-Pro-Arg-Asn-Pro-His-Lys-Gly-Pro-Ala-Thr-OH; Rt = 24.6; M<sup>+</sup> = 1835;

of H-Pro-His(Trt)-Lys(Boc)-Gly-Pro-Ala-Thr(But)-Wang resin with Fmoc-Gly-Lys(Boc)-Thr(But)-Cys(Trt)-Asp(Obut)-Cys(Trt)-Pro-Arg(Mtr)-Asn(Trt)-OH:

20 H-Gly-Lys-Thr-Cys(Trt)-Asp-Cys(Trt)-Pro-Arg-Asn-Pro-His-Lys-Gly-Pro-Ala-Thr-OH; Rt = 30.8; M<sup>+</sup> = 2167;

of H-Pro-His(Trt)-Lys(Boc)-Gly-Wang resin with Fmoc-Gly-Lys(Boc)-Thr(But)-Ala-Asp(Obut)-Cys(Trt)-Pro-Arg(Mtr)-Asn(Trt)-OH:

25 H-Gly-Lys-Thr-Ala-Asp-Cys(Trt)-Pro-Arg-Asn-Pro-His-Lys-Gly-OH; Rt = 24.5; M<sup>+</sup> = 1623;

of H-Pro-His(Trt)-Lys(Boc)-Gly-Pro-Ala-Thr(But)-Wang resin with Fmoc-Thr(But)-Ala-Asp(Obut)-Cys(Trt)-Pro-Arg(Mtr)-Asn(Trt)-OH:

30 H-Thr-Ala-Asp-Cys-Pro-Arg-Asn-Pro-His-Lys-Gly-Pro-Ala-Thr-OH; Rt = 24.9; M<sup>+</sup> = 1707.

### Example 13

By analogy with Examples 7 and 8, the following are obtained by condensation and subsequent hydrolysis,

35 and removal of the BOC protective group, starting

from H-Pro-His(Trt)-Lys(Boc)-Gly-Pro-Ala-Thr(But)-OMe

with Boc-Ala-Asp(Obut)-Cys(Trt)-Pro-Arg(Mtr)-Asn(Trt)-OH:

H-Ala-Asp-Cys-Pro-Arg-Asn-Pro-His-Lys-Gly-Pro-Ala-

Thr-OH; Rt = 13.1; M<sup>+</sup> = 1362;  
 from H-Pro-His(Trt)-Lys(Boc)-Gly-OMe with Boc-Ala-  
 Asp(OMe)-Cys(Trt)-Pro-Arg(Mtr)-Asn(Trt)-OH:  
 H-Ala-Asp-Cys-Pro-Arg-Asn-Pro-His-Lys-Gly-OH; Rt =  
 5 10.6; M<sup>+</sup> = 1094;  
 from H-Pro-His(Trt)-Lys(Boc)-Gly-OMe with Boc-Gly-  
 Lys(Boc)-Thr(But)-Ala-Asp(OMe)-Cys(Trt)-Pro-Arg(Mtr)-  
 Asn(Trt)-OH:  
 H-Gly-Lys-Thr-Ala-Asp-Cys-Pro-Arg-Asn-Pro-His-Lys-  
 10 Gly-OH; Rt = 11.4; M<sup>+</sup> = 1380;  
 from H-Pro-His(Trt)-Lys(Boc)-Gly-Pro-Ala-Thr(But)-OMe  
 with Boc-Lys(Boc)-Thr(But)-(Ala-Asp(OMe)-Cys(Trt)-Pro-  
 Arg(Mtr)-Asn(Trt)-OH:  
 H-Lys-Thr-Ala-Asp-Cys-Pro-Arg-Asn-Pro-His-Lys-Gly-  
 15 Pro-Ala-Thr-OH; Rt = 12.7; M<sup>+</sup> = 1592.

Example 14

By analogy with Example 2, the following are obtained starting from Fmoc-Asp(OMe)-DMPP resin, after carrying out the appropriate reaction steps:  
 20 by coupling with Fmoc-Ala-OH, Fmoc-Thr(But)-OH and Fmoc-Lys(Boc)-OH in the specified sequence:  
 Fmoc-Lys(Boc)-Thr(But)-Ala-Asp(OMe)-OH.  
 The following are obtained analogously, starting from Fmoc-Cys(Trt)-DMPP resin  
 25 by coupling with Fmoc-Asp(OMe)-OH in the specified sequence:  
 Fmoc-Asp(OMe)-Cys(Trt)-OH;  
 by coupling with Fmoc-Asp(OMe)-OH and Fmoc-Ala-OH in the specified sequence:  
 30 Fmoc-Ala-Asp(OMe)-Cys(Trt)-OH;  
 by coupling with Fmoc-Asp(OMe)-OH, Fmoc-Ala-OH and Fmoc-Thr(But)-OH in the specified sequence:  
 Fmoc-Thr(But)-Ala-Asp(OMe)-Cys(Trt)-OH.

Example 15

35 By analogy with Example 1, starting from H-Pro-Wang resin and by condensation with Fmoc-Asn(Trt)-OH, Fmoc-Arg(Mtr)-OH, Fmoc-Pro-OH and Fmoc-Cys(Trt)-OH in the

specified sequence in a peptide synthesizer (continuous flow principle), after repeating the steps indicated above, Fmoc-Cys(Trt)-Pro-Arg(Mtr)-Asn(Trt)-Pro-Wang resin is obtained, which is retreated with piperidine/DMF (20%) 5 to give H-Cys(Trt)-Pro-Arg(Mtr)-Asn(Trt)-Pro-Wang resin.

The following are obtained analogously, starting from Fmoc-Lys(Boc)-Wang resin by coupling with Fmoc-His(Trt)-OH, Fmoc-Pro-OH, Fmoc-Asn(Trt)-OH, Fmoc-Arg(Mtr)-OH, Fmoc-Pro-OH and Fmoc-Cys(Trt)-OH in the 10 specified sequence:

H-Cys(Trt)-Pro-Arg(Mtr)-Asn(Trt)-Pro-His(Trt)-Lys(Boc)-Wang resin;  
from Fmoc-His(Trt)-Wang resin by coupling with Fmoc-Pro-OH, Fmoc-Asn(Trt)-OH, Fmoc-Arg(Mtr)-OH, Fmoc-Pro-OH and 15 Fmoc-Cys(Trt)-OH in the specified sequence:

H-Cys(Trt)-Pro-Arg(Mtr)-Asn(Trt)-Pro-His(Trt)-Wang resin;  
from Fmoc-Gly-Wang resin by coupling with Fmoc-Lys(Boc)-OH, Fmoc-His(Trt)-OH, Fmoc-Pro-OH, Fmoc-Asn(Trt)-OH, 20 Fmoc-Arg(Mtr)-OH, Fmoc-Pro-OH and Fmoc-Cys(Trt)-OH in the specified sequence:

H-Cys(Trt)-Pro-Arg(Mtr)-Asn(Trt)-Pro-His(Trt)-Lys(Boc)-Gly-Wang resin;  
from Fmoc-Arg(Mtr)-Wang resin by coupling with Fmoc-Pro-OH and Fmoc-Cys(Trt)-OH in the specified sequence: 25 H-Cys(Trt)-Pro-Arg(Mtr)-Wang resin;  
from Fmoc-Ala-Wang resin by coupling with Fmoc-Cys(Trt)-OH:  
H-Cys(Trt)-Ala-Wang resin.

30 Example 16  
By analogy with Example 5, by condensation of Fmoc-Lys(Boc)-Thr(But)-Ala-Asp(Obut)-OH with H-Cys(Trt)-Pro-Arg(Mtr)-Asn(Trt)-Pro-Wang resin, Fmoc-Lys(Boc)-Thr(But)-Ala-Asp(Obut)-Cys(Trt)-Pro-Arg(Mtr)-Asn(Trt)-35 Pro-Wang resin is obtained. Subsequent treatment with TFA/CH<sub>2</sub>Cl<sub>2</sub>, followed by removal of the Fmoc group with piperidine/DMF (20%) gives:  
H-Lys-Thr-Ala-Asp-Cys(Trt)-Pro-Arg-Asn-Pro-OH; R<sub>t</sub> = 25.4;

$M^* = 1243$ .

The following are obtained by condensation of Fmoc-Lys(Boc)-Thr(But)-Ala-Asp(Obut)-OH with H-Cys(Trt)-Pro-Arg(Mtr)-Asn(Trt)-Pro-His(Trt)-Lys(Boc) -

5 Wang resin:

H-Lys-Thr-Ala-Asp-Cys(Trt)-Pro-Arg-Asn-Pro-His-Lys-OH; Rt = 23.6;  $M^* = 1509$ ;

of Fmoc-Lys(Boc)-Thr(But)-Ala-Asp(Obut)-OH with H-Cys(Trt)-Pro-Arg(Mtr)-Asn(Trt)-Pro-His(Trt)-Wang resin:

10 H-Lys-Thr-Ala-Asp-Cys(Trt)-Pro-Arg-Asn-Pro-His-OH; Rt = 24.3;  $M^* = 1380$ ;

of Fmoc-Lys(Boc)-Thr(But)-Ala-Asp(Obut)-OH with H-Cys(Trt)-Pro-Arg(Mtr)-Asn(Trt)-Pro-His(Trt)-Lys(Boc)-Gly-Wang resin:

15 H-Lys-Thr-Ala-Asp-Cys(Trt)-Pro-Arg-Asn-Pro-His-Lys-Gly-OH; Rt = 23.7;  $M^* = 1565$ ;

of Fmoc-Lys(Boc)-Thr(But)-Ala-Asp(Obut)-OH with H-Cys(Trt)-Pro-Arg(Mtr)-Wang resin:

H-Lys-Thr-Ala-Asp-Cys(Trt)-Pro-Arg-OH; Rt = 25.7;

20  $M^* = 1032$ ;

of Fmoc-Asp(Obut)-Cys(Trt)-OH with H-Pro-Arg(Mtr)-Asn(Trt)-Pro-His(Trt)-Lys(Boc)-Wang resin:

H-Asp-Cys(Trt)-Pro-Arg-Asn-Pro-His-Lys-OH;

of Fmoc-Ala-Asp(Obut)-Cys(Trt)-OH with H-Pro-Arg(Mtr) -

25 Wang resin:

H-Ala-Asp-Cys(Trt)-Pro-Arg-OH; Rt = 27.4;  $M^* = 803$ ;

of Fmoc-Thr(But)-Ala-Asp(Obut)-Cys(Trt)-OH with H-Pro-Arg(Mtr)-Wang resin:

H-Thr-Ala-Asp-Cys(Trt)-Pro-Arg-OH; Rt = 27.3;

30  $M^* = 904$ ;

of Fmoc-Lys(Boc)-Thr(But)-Ala-Asp(Obut)-OH with H-Cys(Trt)-Pro-Wang resin:

H-Lys-Thr-Ala-Asp-Cys(Trt)-Pro-OH.

#### Example 17

35 0.9 g of H-Cys(Trt)-Pro-Arg-Asn-Pro-His-Lys(BOC)-DMPP resin [prepared as in Example 1] is dissolved in 100 ml of dichloromethane, condensed with H<sub>2</sub>-CO-Asp-OH by analogy with Example 2, and worked up. Reintroduction of

the Trt group using triphenylmethanol gives H<sub>3</sub>C-CO-Asp-Cys(Trt)-Pro-Arg-Asn-Pro-His-Lys-OH; Rt = 26.0; M<sup>+</sup> = 1250.

5 The following are obtained analogously, starting from H-Thr-Ala-Asp-Cys(Trt)-Pro-OH with H<sub>3</sub>C-CO-Lys(BOC)-OH:

H<sub>3</sub>C-CO-Lys-Thr-Ala-Asp-Cys(Trt)-Pro-OH;

from H-Ser-Ala-Asp-Cys(Trt)-Pro-OH with H<sub>3</sub>CO-Gln(Trt)-OH:

H<sub>3</sub>C-CO-Gln-Ser-Ala-Asp-Cys(Trt)-Pro-OH.

10 Example 18

0.7 g of Fmoc-Cys(Trt)-Pro-OH is dissolved in 100 ml of dichloromethane; 1.4 equivalents of MBHA resin, 1.4 equivalents of HOBr and 1.4 equivalents of DCC are added, and the mixture is stirred at room temperature for 24 hours. After removal of the solvent Fmoc-Cys(Trt)-Pro-MBHA resin is obtained. By treatment (at room temperature for 1 hour) with piperidine/DMF (20%) this gives H-Cys(Trt)-Pro-MBHA resin, which is subsequently coupled with Fmoc-Lys(Boc)-Thr(But)-Ala-Asp(OBut)-OH by adding 20 the threefold excess of this compound. The coupling is carried out at room temperature in DCCI/HOBr, to give Fmoc-Lys(Boc)-Thr(But)-Ala-Asp(OBut)-Cys(Trt)-Pro-MBHA resin. Subsequent retreatment with piperidine/DMF (20%) gives H-Lys(Boc)-Thr(But)-Ala-Asp(OBut)-Cys(Trt)-Pro-MBHA 25 resin.

The resulting compound is taken up in 20 ml of TFA and stirred at room temperature for 2 hours. Conventional purification gives H-Lys-Thr-Ala-Asp-Cys(Trt)-Pro-NH<sub>2</sub>.

30 The following peptide amides are obtained analogously, by reacting the free peptides with MBHA resin and then removing the resin:

H-Lys-Thr-Ala-Asp-Cys(Trt)-Pro-Arg-Asn-Pro-His-Lys-NH<sub>2</sub>;

H-Lys-Thr-Ala-Asp-Cys(Trt)-Pro-Arg-Asn-Pro-His-NH<sub>2</sub>;

H-Lys-Thr-Ala-Asp-Cys(Trt)-Pro-Arg-Asn-Pro-His-Lys-Gly-NH<sub>2</sub>;

H-Lys-Thr-Ala-Asp-Cys(Trt)-Pro-Arg-NH<sub>2</sub>;

H-Asp-Cys(Trt)-Pro-Arg-Asn-Pro-His-Lys-NH<sub>2</sub>;

H-Ala-Asp-Cys(Trt)-Pro-Arg-NH<sub>2</sub>;  
H-Thr-Ala-Asp-Cys(Trt)-Pro-Arg-NH<sub>2</sub>;  
H-Lys-Thr-Ala-Asp-Cys(Trt)-Pro-NH<sub>2</sub>.

Example 19

By analogy with Example 17, by condensation of H-Thr-Ala-Asp-Cys(Trt)-Pro-NH<sub>2</sub> with H<sub>3</sub>C-CO-Lys(BOC)-OH followed by removal of the BOC group, H<sub>3</sub>C-CO-Lys-Thr-Ala-  
5 Asp-Cys(Trt)-Pro-NH<sub>2</sub>, is obtained.

The following are obtained analogously:

H<sub>3</sub>C-CO-Lys-Thr-Ala-Asp-Cys(Trt)-Pro-Arg-Asn-Pro-His-Lys-NH<sub>2</sub>;  
H<sub>3</sub>C-CO-Lys-Thr-Ala-Asp-Cys(Trt)-Pro-Arg-Asn-Pro-His-Lys-Gly-NH<sub>2</sub>;  
H<sub>3</sub>C-CO-Lys-Thr-Ala-Asp-Cys(Trt)-Pro-Arg-NH<sub>2</sub>;  
H<sub>3</sub>C-CO-Thr-Ala-Asp-Cys(Trt)-Pro-Arg-NH<sub>2</sub>;  
H<sub>3</sub>C-CO-Lys-Thr-Ala-Asp-Cys(Trt)-Pro-NH<sub>2</sub>.

Example 20

By analogy with Example 5, by condensation of Fmoc-Lys(Boc)-Thr(But)-Ala-Asp(BOBut)-OH with H-Cys(Trt)-  
10 NMeAla-Wang resin, Fmoc-Lys(Boc)-Thr(But)-NMeAla-Wang resin is obtained. Subsequent treatment with TFA/CH<sub>2</sub>Cl<sub>2</sub>, followed by removal of the Fmoc group with piperidine/DMF (20%) gives:  
H-Lys-Thr-Ala-Asp-Cys(Trt)-NMeAla-OH.

Example 21

0.2 g of H-Lys-Thr-Ala-Asp-Cys-Pro-Arg-Asn-Pro-His-Lys-Gly-OH is dissolved in 30 ml of CH<sub>2</sub>Cl<sub>2</sub>, and 30 ml of TFA, and 1.2 equivalents of triphenylmethyl alcohol are added thereto at room temperature. The mixture is subsequently stirred for an hour and the peptide formed is precipitated, after concentration, by addition of diethyl ether. Conventional purification gives H-Lys-Thr-Ala-Asp-Cys(Trt)-Pro-Arg-Asn-Pro-His-Lys-Gly-OH;

Rt = 23.7; M<sup>+</sup> = 1565.

The following are obtained analogously by alkylation of H-Lys-Thr-Ala-Asp-Cys-Pro-Arg-Asn-Pro-His-Lys-Gly-OH:

- 5 with methyl iodide: H-Lys-Thr-Ala-Asp-Cys(Me)-Pro-Arg-Asn-Pro-His-Lys-Gly-OH; Rt = 9.8; M<sup>+</sup> = 1338;
- with ethyl iodide: H-Lys-Thr-Ala-Asp-Cys(Et)-Pro-Arg-Asn-Pro-His-Lys-Gly-OH; Rt = 10.4; M<sup>+</sup> = 1352;
- with benzyl chloride: H-Lys-Thr-Ala-Asp-Cys(Bzl)-Pro-Arg-Asn-Pro-His-Lys-Gly-OH; Rt = 13.8; M<sup>+</sup> = 1415;
- 10 with tert-butyl chloride: H-Lys-Thr-Ala-Asp-Cys(tBu)-Pro-Arg-Asn-Pro-His-Lys-Gly-OH; Rt = 12.3; M<sup>+</sup> = 1379;
- with diphenylmethyl chloride:  
H-Lys-Thr-Ala-Asp-Cys(Dpm)-Pro-Arg-Asn-Pro-His-Lys-Gly-OH; Rt = 17.8; M<sup>+</sup> = 1489.

The examples below relate to pharmaceutical formulations.

#### Example A: Injection vials

A solution 100 g of an active substance of the formula I and 5 g of disodium hydrogen phosphate in 3 l of double-distilled water is adjusted to a pH of 6.5 using 2N hydrochloric acid, sterilized by filtration, used to fill injection vials and then lyophilized under sterile conditions, and the vials are sealed under sterile conditions. Each injection vial contains 5 mg of active substance.

#### Example B: Suppositories

A mixture of 20 g of an active substance of the formula I together with 100 g of soya lecithin and 1400 g of cocoa butter is melted, poured into moulds and left to cool. Each suppository contains 20 mg of active substance.

#### Example C: Solution

A solution is prepared from 1 g of an active substance of the formula I, 9.38 g of NaH<sub>2</sub>PO<sub>4</sub> × 2H<sub>2</sub>O,

28.48 g of  $\text{Na}_2\text{HPO}_4 \times 12 \text{ H}_2\text{O}$  and 0.1 g of benzalconium chloride in 940 ml of double-distilled water. The solution is adjusted to a pH of 6.8, made up to 1 l and sterilized by irradiation. This solution can be used in 5 the form of eye drops.

**Example D: Ointment**

500 mg of an active substance of the formula I is mixed with 99.5 g of petroleum jelly under aseptic conditions.

10 **Example E: Tablets**

A mixture 1 kg of active substance of formula I, 4 kg of lactose, 1.2 kg of potato starch, 0.2 kg of talc and 0.1 kg of magnesium stearate is compressed in a customary manner to form tablets such that each tablet 15 contains 10 mg of active substance.

**Example F: Coated tablets**

By analogy with Example E tablets are moulded, and are then coated in a conventional manner with a coating comprising saccharose, potato starch, talc, 20 tragacanth and colorant.

**Example G: Capsules**

Hard gelatin capsules are filled, in a customary manner, with 2 kg of active substance of the formula I, so that each capsule contains 20 mg of the active substance. 25

**Example H: Ampoules**

A solution of 1 kg of active substance of the formula I in 60 l of double-distilled water is filtered sterile, dispensed into ampoules and lyophilized under 30 sterile conditions, and the ampoules are sealed under sterile conditions. Each ampoule contains 10 mg of active substance.

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Patent claims

5 1. Linear peptides of the formula I

X-A-Cys(R<sup>1</sup>)-B-Z I,

in which

X is H or Ac,

A is absent or is Asp or a peptide fragment selected  
10 from a group consisting of Ala-Asp, Thr-Ala-Asp,  
Lys-Thr-Ala-Asp, Lys-Thr-Ala-Asn, Lys-Thr-Gly-Asp,  
Lys-Ala-Ala-Asp, Arg-Thr-Ala-Asp, Ser-Ala-Asp,  
Gln-Ser-Ala-Asp, Gly-Lys-Thr-Ala-Asp,  
Asn-Gly-Lys-Thr-Ala-Asp, Ile-Ser-Ala-Gly,  
15 Arg-Ser-Ala-Gly, Cys-Asn-Gly-Lys-Thr-Ala-Asp;  
Tyr-Cys-Asn-Gly-Lys-Thr-Ala-Asp,  
Asp-Tyr-Cys-Asn-Gly-Lys-Thr-Ala-Asp,  
Gly-Lys-Thr-Cys-Asp,  
Asp-Asp-Tyr-Cys-Asn-Gly-Lys-Thr-Ala-Asp,  
20 Gly-Lys-Thr-Cys(Trt)-Asp,  
Met-Asp-Asp-Tyr-Cys-Asn-Gly-Lys-Thr-Ala-Asp and  
Asp-Met-Asp-Asp-Tyr-Cys-Asn-Gly-Lys-Thr-Ala-Asp,  
B is absent or is Ala, Arg, Asn, Asp, Cys, Gln, Glu,  
Gly, His, Ile, Leu, Lys, Met, Orn, Phe, 4-Hal-Phe,  
25 Pro, Ser, Thr, Trp, Tyr or Val or is an N-methylated  
derivative of the amino acid residues mentioned, or  
is a peptide fragment selected from the group  
consisting of Pro-Arg, Pro-Arg-Asn, Pro-Arg-Asn-Pro,  
Pro-Arg-Asn-Pro-His, Pro-Arg-Asn-Pro-His-Lys,  
30 Pro-Arg-Asn-Pro-His-Lys-Gly,  
Pro-Arg-Asn-Pro-His-Lys-Gly-Pro,  
Pro-Arg-Asn-Pro-His-Lys-Gly-Pro-Ala and  
Pro-Arg-Asn-Pro-His-Lys-Gly-Pro-Ala-Thr,  
in which only one of the residues A or B can be absent,  
35 Z is OH, OR<sup>2</sup>, NH<sub>2</sub>, NHR<sup>2</sup> or NR<sup>2</sup>,

R<sup>1</sup> is H, R<sup>2</sup>, Trt, Dpm or Bzl,

R<sup>2</sup> is alkyl of 1-6 carbon atoms,

Hal is F, Cl, Br or I and

Ac is alkanoyl of 1-10 carbon atoms, aralkanoyl of 8-10  
5 carbon atoms or aroyl of 7-11 carbon atoms,  
and to their physiologically acceptable salts.

2. An enantiomer or a diastereomer of a compound of  
the formula I according to Claim 1.

3. (a) H-Ala-Asp-Cys(Trt)-Pro-Arg-Asn-Pro-His-Lys-

10 Gly-Pro-Ala-Thr-OH;

(b) H-Lys-Thr-Ala-Asp-Cys(Trt)-Pro-Arg-Asn-Pro-His-Lys-  
Gly-Pro-Ala-Thr-OH;

(c) H-Gly-Lys-Thr-Ala-Asp-Cys(Trt)-Pro-Arg-Asn-Pro-His-  
Lys-Gly-OH;

15 (d) H-Lys-Thr-Ala-Asp-Cys(Trt)-Pro-Arg-Asn-Pro-His-OH;

(e) H-Lys-Thr-Ala-Asp-Cys(Trt)-Pro-Arg-Asn-Pro-His-Lys-  
Gly-OH;

(f) H-Lys-Thr-Ala-Asp-Cys(Trt)-Pro-Arg-OH;

(g) H-Lys-Thr-Ala-Asp-Cys(Trt)-Pro-OH and

20 (h) H<sub>3</sub>C-CO-Asp-Cys(Trt)-Pro-Arg-Asn-Pro-His-Lys-OH.

4. Process for the preparation of a compound of the  
formula I according to Claim 1 or of one of its salts,  
characterized in that it is liberated from one of its  
functional derivatives by treatment with a solvolyzing or  
25 hydrogenolyzing agent or in that a compound of formula II

X-M-OH

II

in which

M is an amino acid residue or peptide radical selected  
from a group consisting of A, A-Cys(R<sup>1</sup>),

Ala, Thr, Thr-Ala, Lys, Lys-Thr, Lys-Thr-Ala, Gly,

Lys-Thr-Ala-Gly, Gly-Lys, Gly-Lys-Thr, Gly-Lys-Thr-Ala,

Gly-Lys-Thr-Cys(R<sup>1</sup>), Asn, Asn-Gly, Asn-Gly-Lys, Lys-Ala, Lys-Ala-Ala,

Asn-Gly-Lys-Thr, Asn-Gly-Lys-Thr-Ala, Cys, Cys-Asn, Cys-Asn-Gly, Arg,

Arg-Thr, Arg-Thr-Ala, Ser, Cys-Asn-Gly-Lys, Cys-Asn-Gly-Lys-Thr,

Cys-Asn-Gly-Lys-Thr-Ala, Ser-Ala, Tyr, Tyr-Cys, Tyr-Cys-Asn,

Tyr-Cys-Asn-Gly, Tyr-Cys-Asn-Gly-Lys, Gln, Gln-Ser, Gln-Ser-Ala,

Tyr-Cys-Asn-Gly-Lys-Thr, Tyr-Cys-Asn-Gly-Lys-Thr-Ala, Asp, Asp-Tyr,

Asp-Tyr-Cys, Asp-Tyr-Cys-Asn, Asp-Tyr-Cys-Asn-Gly, Ile, Ile-Ser,

Ile-Ser-Ala, Asp-Tyr-Cys-Asn-Gly-Lys, Asp-Tyr-Cys-Asn-Gly-Lys-Thr,  
 Arg-Ser, Arg-Ser-Ala, Asp-Tyr-Cys-Asn-Gly-Lys-Thr-Ala, Asp-Asp,  
 Asp-Asp-Tyr, Asp-Asp-Tyr-Cys, Asp-Asp-Tyr-Cys-Asn,  
 Asp-Asp-Tyr-Cys-Asn-Gly, Asp-Asp-Tyr-Cys-Asn-Gly-Lys,  
 Asp-Asp-Tyr-Cys-Asn-Gly-Lys-Thr,  
 Asp-Asp-Tyr-Cys-Asn-Gly-Lys-Thr-Ala, Met, Met-Asp, Met-Asp-Asp,  
 Met-Asp-Asp-Tyr, Met-Asp-Asp-Tyr-Cys, Met-Asp-Asp-Tyr-Cys-Asn,  
 Met-Asp-Asp-Tyr-Cys-Asn-Gly, Met-Asp-Asp-Tyr-Cys-Asn-Gly-Lys,  
 Met-Asp-Asp-Tyr-Cys-Asn-Gly-Lys-Thr,  
 Met-Asp-Asp-Tyr-Cys-Asn-Gly-Lys-Thr-Ala, Asp-Met, Asp-Met-Asp,  
 Asp-Met-Asp-Asp, Asp-Met-Asp-Asp-Tyr, Asp-Met-Asp-Asp-Tyr-Cys,  
 Asp-Met-Asp-Asp-Tyr-Cys-Asn, Asp-Met-Asp-Asp-Tyr-Cys-Asn-Gly,  
 Asp-Met-Asp-Asp-Tyr-Cys-Asn-Gly-Lys,  
 Asp-Met-Asp-Asp-Tyr-Cys-Asn-Gly-Lys-Thr,  
 Asp-Met-Asp-Asp-Tyr-Cys-Asn-Gly-Lys-Thr-Ala, A-Cys(R<sup>1</sup>)-Pro,  
 A-Cys(R<sup>1</sup>)-Pro-Arg, A-Cys(R<sup>1</sup>)-Pro-Arg-Asn, A-Cys(R<sup>1</sup>)-Pro-Arg-Asn-Pro,  
 A-Cys(R<sup>1</sup>)-Pro-Arg-Asn-Pro-His, A-Cys(R<sup>1</sup>)-Pro-Arg-Asn-Pro-His-Lys,  
 A-Cys(R<sup>1</sup>)-Pro-Arg-Asn-Pro-His-Lys-Gly,  
 A-Cys(R<sup>1</sup>)-Pro-Arg-Asn-Pro-His-Lys-Gly-Pro,  
 A-Cys(R<sup>1</sup>)-Pro-Arg-Asn-Pro-His-Lys-Gly-Pro-Ala,  
 in which A and R<sup>1</sup> are as defined in Claim 1,  
 and

**x** is as defined but is not hydrogen if A and therefore  
 M are absent, is reacted with an amino compound of  
 5 the formula III

H-Q-Z

III,

in which

Z is as defined and

Q is an amino acid residue or peptide radical selected  
 10 from a group consisting of B, Cys(R<sup>1</sup>)-B,

Arg-Asn, Arg-Asn-Pro, Asn-Pro, Arg-Asn-Pro-His,  
 Asn-Pro-His, Pro-His, Arg-Asn-Pro-His-Lys, Asn-Pro-His-Lys,  
 Pro-His-Lys, His-Lys, Arg-Asn-Pro-His-Lys-Gly, Asn-Pro-His-Lys-Gly,  
 Pro-His-Lys-Gly, His-Lys-Gly, Lys-Gly, Arg-Asn-Pro-His-Lys-Gly-Pro,  
 Asn-Pro-His-Lys-Gly-Pro, Pro-His-Lys-Gly-Pro, His-Lys-Gly-Pro,  
 Lys-Gly-Pro, Gly-Pro, Arg-Asn-Pro-His-Lys-Gly-Pro-Ala,  
 Asn-Pro-His-Lys-Gly-Pro-Ala, Pro-His-Lys-Gly-Pro-Ala,

His-Lys-Gly-Pro-Ala, Lys-Gly-Pro-Ala, Gly-Pro-Ala, Pro-Ala,  
Arg-Asn-Pro-His-Lys-Gly-Pro-Ala-Thr, Asn-Pro-His-Lys-Gly-Pro-Ala-Thr,  
Pro-His-Lys-Gly-Pro-Ala-Thr, His-Lys-Gly-Pro-Ala-Thr,  
Lys-Gly-Pro-Ala-Thr, Gly-Pro-Ala-Thr, Pro-Ala-Thr, Ala-Thr,  
Gly-Asp-Cys(R<sup>1</sup>)-B, Thr-Gly-Asp-Cys(R<sup>1</sup>)-B, Asp-Cys(R<sup>1</sup>)-B,  
Ala-Asp-Cys(R<sup>1</sup>)-B, Thr-Ala-Asp-Cys(R<sup>1</sup>)-B, Lys-Thr-Ala-Asp-Cys(R<sup>1</sup>)-B,  
Gly-Lys-Thr-Ala-Asp-Cys(R<sup>1</sup>)-B, Asn-Gly-Lys-Thr-Ala-Asp-Cys(R<sup>1</sup>)-B,  
Asn-Cys(R<sup>1</sup>)-B, Ala-Asn-Cys(R<sup>1</sup>)-B, Thr-Ala-Asn-Cys(R<sup>1</sup>)-B,  
Cys-Asn-Gly-Lys-Thr-Ala-Asp-Cys(R<sup>1</sup>)-B, Ala-Ala-Asp-Cys(R<sup>1</sup>)-B,  
Ser-Ala-Asp-Cys(R<sup>1</sup>)-B, Tyr-Cys-Asn-Gly-Lys-Thr-Ala-Asp-Cys(R<sup>1</sup>)-B,  
Gly-Cys(R<sup>1</sup>)-B, Ala-Gly-Cys(R<sup>1</sup>)-B, Ser-Ala-Gly-Cys(R<sup>1</sup>)-B,  
Cys(Trt)-Asp-Cys(R<sup>1</sup>)-B, Thr-Cys(Trt)-Asp-Cys(R<sup>1</sup>)-B,  
Lys-Thr-Cys(Trt)-Asp-Cys(R<sup>1</sup>)-B,  
Asp-Tyr-Cys-Asn-Gly-Lys-Thr-Ala-Asp-Cys(R<sup>1</sup>)-B,  
Asp-Asp-Tyr-Cys-Asn-Gly-Lys-Thr-Ala-Asp-Cys(R<sup>1</sup>)-B or  
Met-Asp-Asp-Tyr-Cys-Asn-Gly-Lys-Thr-Ala-Asp-Cys(R<sup>1</sup>)-B

in which R<sup>1</sup> is as defined,

and/or in that a free mercapto, hydroxyl or amino group  
is alkylated

and/or a compound of the formula I according to Claim 1  
5 is converted into one of its salts by treatment with an  
acid or base.

5. Process for the preparation of pharmaceutical  
formulations, characterized in that a compound of the  
formula I according to Claim 1 and/or one of its physio-  
10 logically acceptable salts, together with at least one  
solid, liquid or semiliquid excipient or auxiliary, is  
brought into a suitable administration form.

6. Pharmaceutical formulation, characterized in that  
it contains at least one compound of the general formula  
15 I according to Claim 1 and/or one of its physiologically  
acceptable salts.

7. Use of compounds of the formula I according to  
Claim 1 or of physiologically acceptable salts thereof  
for the preparation of a medicament for combating  
20 diseases.

8. Use of compounds of the formula I according to

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- 5 -

Claim 1 or of physiologically acceptable salts thereof in the combating of diseases.

9. Use of compounds of the formula I according to Claim 1 for the preparation of immobilized ligands for 5 affinity column chromatography.

10. Use of compounds of the formula I according to Claim 1 for the purification of integrins by affinity chromatography.

Fetherstonhaugh & Co.,  
Ottawa, Canada  
Patent Agents

**SUBSTITUTE**

***REEMPLACEMENT***

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